REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative at 858 720 5133.

The Advisory Action

In box 3, of the Advisory Action (mailed December 01, 2005) (see continuation sheet), it was noted that the Exhibits A through H were received (as submitted in Applicants' last response).

In box 3, it was noted that Applicants' amendment in their "after final" response of October 31, 2005, was not entered because, inter alia, the new claims have not been examined before and may require further consideration and/or search. Accordingly, the instant amendments are based on the last entered claim set, i.e., the claim set as set forth in Applicants' response of April 11, 2005.

In box 5, of the Advisory Action, it was noted that Applicants' reply of October 31, 2005, when entered, would overcome the rejection of claims 31, 32, 36, 37, 49 and 52 to 65, under section 112, first paragraph.

Status of the Claims

Pending claims

Claims 31, 32, 36, 37, 44 and 49 to 65 are pending.

Claims only objected to

Applicants thank the Examiner for noting that claims 51, 53 and 62 to 65 are objected to for depending on rejected claims.

Claims added in the instant amendment

In the present response, claims 66 to 80 are added. Accordingly, after entry of the instant amendment, claims 31, 32, 36, 37, 44 and 49 to 80 will be pending and under examination.

Outstanding Objections and Rejections

In box 5, of the Advisory Action, it was noted that Applicants' reply of October 31, 2005, when entered, would overcome the rejection of claims 31, 32, 36, 37, 49 and 52 to 65, under section 112, first paragraph. Thus, assuming entry of Applicants' reply of October 31, 2005, in this RCE, only the rejection of pending claims 44 and 50 is maintained under 35 U.S.C. §112, first paragraph, enablement requirement. As noted by the Advisory Action, the Office has yet to examine the new claims on their merits.

Applicants respectfully traverse all outstanding objections and rejections of the claims.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the pending and amended claims. For example, support for claims directed to methods comprising use of polypeptide or nucleic acid sequences having various sequence identities at or above about 70%, 80%, 85%, 90%, 95% or 97%, or more, to exemplary sequences of the invention can be found, inter alia, on page 11, lines 20 to 30; page 42, lines 5 to 23. Support for claims directed to methods for stereoselectively producing an alpha-substituted carboxylic acid, said method comprising contacting an aldehyde or ketone with a cyanide-containing compound and an ammonia- containing compound, an ammonium salt or an amine, and hydrolyzing stereoselectively the resulting amino nitrile or cyanohydrin intermediate with a nitrilase, wherein the nitrilase is encoded by a nucleic acid that hybridizes under stringent conditions to a sequence as set forth in SEQ ID NO:1 or SEQ ID NO:3, and the stringent hybridization conditions comprise a wash step under specific conditions, can be found, inter alia, on page 39, lines 8 to 19; and see also page 40, line 5 to page 42, line 4. Support for claims directed to methods for stereoselectively producing an alpha-substituted carboxylic acid, said method comprising using a nitrilase having an amino acid sequence as set forth in SEQ ID NO:2 or SEQ ID NO:4, and having at least one conservative amino acid substitution from the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4 can be found, inter alia, on page 11, lines 1 to 18. Support for claims directed to methods for stereoselectively producing an alpha-substituted carboxylic acid, wherein the carboxylic acid has various substituent groups, can be found, inter alia, from page 3, line 14, page 5, line 14.

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Claim Objections

Claims 51, 53 and 62 to 65 are objected to for depending on rejected claims. The instant amendment addresses this issue.

Issues under 35 U.S.C. § 112, First Paragraph - Enablement

In box 5, of the Advisory Action, it was noted that Applicants' reply of October 31, 2005, when entered, would overcome the rejection of claims 31, 32, 36, 37, 49 and 52 to 65, under section 112, first paragraph. Thus, assuming entry of Applicants' reply of October 31, 2005, in this RCE, only the rejection of pending independent claims 44 and 50 is maintained under 35 U.S.C. §112, first paragraph, enablement requirement. As noted by the Advisory Action, the Office has yet to examine the new claims on their merits. Thus, the response as submitted in Applicants' reply of October 31, 2005, is repeated herein as a reply to the maintained enablement rejection of pending independent claims 44 and 50.

Producing alpha-substituted carboxylic acids

The Office maintained the rejection of claims 44 and 50, under 35 U.S.C. §112, first paragraph, enablement requirement, because the specification allegedly does not provide reasonable enablement for methods to produce any alpha-substituted carboxylic acid.

The Office stated that the specification is enabling for methods using SEQ ID NO:2 or SEQ ID NO:4 to stereoselectively produce (S)-phenylglycine from phenylglycinonitrile, or benzaldehyde, KCN or NH_4Cl.

While Applicants respectfully traverse for reasons set forth in previous responses, all expressly incorporated herein, to expedite prosecution and issuance of the pending claims, the instant amendment also addresses this issue. For example, the appropriate claims have been amended to encompass methods for producing alpha-substituted carboxylic acids having a specific structure, as expressly set forth as a claim limitation.

Methods using a genus of nitrilases

The Office maintained the rejection of claims 44 and 50, under 35 U.S.C. §112, first paragraph, enablement requirement, because the specification allegedly does not provide reasonable enablement for methods using a genus of nitrilase enzymes having 70% sequence identity to SEQ ID NO:2 or SEQ ID NO:4.

The Office states that the specification is enabling for methods using SEQ ID NO:2 or SEQ ID NO:4 to stereoselectively produce (S)-phenylglycine from phenylglycinonitrile, or benzaldehyde, KCN or NH_4Cl (see page 6, first paragraph of section 15, of the final OA). The Office also states that the specification provides enough guidance for one of skill in the art to randomly mutate and screen for nitrilase activity (see page 7, lines 1 to 5, of the final OA).

However, the Office remains concerned as to whether the specification enabled the skilled artisan to find the invention – in other words, the Office remains concerned whether with the teaching of the specification it would, or would not, have taken routine experimentation for the skilled artican to screen a group of variant nitrilases to identify enzymes within the scope of the claimed invention, e.g., having at least 70% (or, after entry of this amendment, 80%, 85%, 90% or 95%) sequence identity to the exemplary SEQ ID NO:2 or SEQ ID NO:4. It is alleged, inter alia, that the specification is not reasonably enabled because there is no description in the specification or the art to provide which particular residues within the exemplary sequences are important such that a nitrilase activity is maintained (see, e.g., page 11, lines 1 to 9, of the office action dated November 26, 2004). In other words, it is alleged that without direction as to which residues to change, or not change, only a pool of randomly modified sequences is modified – and this pool would be so large it would have taken undue experimentation to determine which sequences are within the scope of the invention (e.g., having at least 70% sequence identity to the exemplary SEQ ID NO:).

Applicants respectfully aver that the specification enabled the skilled artisan at the time of the invention to make and use, and in particular, to identify or screen for, the claimed genus of nitrilases and nitrilase-encoding polynucleotides without undue experimentation – and have provided evidence and expert declaration to support this argument. See, e.g., Applicants' response

of July 17, 2003, pages 30 to 32, including Dr. Jennifer Chaplin's expert declaration submitted with that response, all expressly incorporated herein. Applicants provide further argument and expert declaration to support this argument in this response.

Applicants also respectfully aver that while methods of screening were sophisticated enough at the time of the invention such that the skilled artisan did not need to know which residues to change, or not change, in fact the prior art and the specification did provide such guidance, and will provide argument and evidence of this guidance.

Scope of the invention and the size of the claimed genus

One of the Office's remaining concerns regards the scope of the invention and the size of the claimed genus. The instant amendment addresses this issue, in part, by presentation of alternative embodiments of the invention – alternative genera of nucleic acids progressively smaller in scope. After entry of the instant amendment, amended claims 44 and 50 and new claims 67 to 70 encompass methods using nitrilases having an amino acid sequence having at least 80%, 85%, 90%, 95% or 97% sequence identity to an amino acid sequence consisting of SEQ ID NO:2 or SEQ ID NO:4, or nitrilases encoded by a nucleic acid having at least 80%, 85%, 90%, 95% or 97% sequence identity to an nucleic acid sequence consisting of SEQ ID NO:1 or SEQ ID NO:3. Applicants respectfully request individual consideration of each of these alternative genera of nitrilase-encoding nucleic acid and nitrilases used in the claimed methods.

A prima facie case of Lack of Enablement has not been made

However, before presenting argument and evidence that the specification sufficiently enabled the skilled artisan to make and use the claimed invention, Applicants respectfully aver that the Patent Office has not met its initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. The art cited by the Office to support its *prima facie* case of lack of enablement is insufficient to rebut the presumptively enabled specification.

In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (Examiner must provide a reasonable explanation as

to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). See also MPEP §2164.04, rev. 2, May 2004, pg 2100-189.

The Patent Office has cited no references to rebut the presumptively enabled specification and has offered no rebuttal to Dr. Jennifer Chaplin's expert declaration submitted with Applicants' response of July 17, 2003. Accordingly, because the Office has not met its initial burden to establish a reasonable basis to question the enablement provided for the claimed invention, a *prima facie* case of lack of enablement has not been made, and the rejection under section 112, first paragraph can be properly withdrawn.

Specification enabled the skilled artisan to make and use the claimed invention

However, assuming *arguendo* that a *prima facie* case of nonenablement was made by the Office, Applicants respectfully maintain that the instant specification does provide reasonable enablement commensurate with the scope of the claimed invention. As noted above, the Office remains concerned whether it would, or would not, have taken routine experimentation to find, or screen for, groups of nitrilases that are variants to the exemplary sequences of the invention to identify enzymes within the scope of the claimed invention, e.g., having at least 70% sequence identity to the exemplary SEQ ID NO:2 or SEQ ID NO:4. It is alleged, inter alia, that the specification is not reasonably enabled because there is no description in the specification or the art to provide which particular residues within the exemplary sequences are important such that a

nitrilase activity is maintained (see, e.g., page 7 of the final OA, or page 11, lines 1 to 9, of the OA dated November 26, 2004).

As presented in Applicants' response of July 17, 2003, the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art, e.g., screening enzymes, and nucleic acids encoding enzymes, for nitrilase activity such that the enzyme produces an alpha-substituted carboxylic acid, was very high. In the expert declaration submitted by co-inventor Dr. Jennifer Ann Chaplin, it would not have taken undue experimentation to make and use the claimed invention, including identification of nitrilases that perform the proper hydrolysis reaction on the proper substrate. Dr. Chaplin declared that at the time of the invention, with the teaching of the specification, it would have taken only routine screening by one skilled in the art to identify recombinant nitrilase enzymes capable of producing an enantiomerically pure alpha-substituted carboxylic acid by combining an aldehyde or ketone with a cyanide and ammonia or an ammonium salt or an amine. Dr. Chaplin declared that that using the teaching of the specification, including the exemplary protocol as set forth in Example 1, pages 77 and 78, of specification, and other protocols known in the art at the time of the invention, alternative protocols, including the protocol set forth in the specification, could have been designed by one skilled in the art at the time of the invention to successfully practice the methods of the invention, e.g., to produce an alpha-substituted carboxylic acid by contacting an aldehyde or ketone with a cyanide-containing compound and an ammonia-containing compound or an ammonium salt or an amine, and hydrolyzing (stereoselectively, in one embodiment) a resulting amino nitrile or cyanohydrin intermediate with a nitrilase of the invention, where the nitrilase is sufficiently active to perform the hydrolysis in the presence of the reaction components, under conditions and for a time sufficient to produce the alpha-substituted carboxylic acid (an enantiomerically pure product in some aspects).

Also as previously discussed, whether large numbers of compositions (e.g., enzymes, antibodies, nucleic acids, and the like) must be screened to determine if one is within the scope of the claimed invention is irrelevant to an enablement inquiry. Enablement is not precluded by the necessity to screen large numbers of compositions, as long as that screening is "routine," i.e., not "undue," to use the words of the Federal Circuit. The Federal Circuit in In re Wands directed that

the focus of the enablement inquiry should be whether the experimentation needed to practice the invention is or is not "undue" experimentation. Guidance as to how much experimentation may be needed and still not be "undue" was set forth by the Federal Circuit in, e.g. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987), which was discussed in Applicants' response of July 17, 2003.

The proper legal test is that the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). See MPEP §2164.08, pg 2100-197, 8th ed., rev. 2, May 2004. 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). MPEP §2164.06, pg 2100-192, 8th ed., rev. 2, May 2004.

The facts in In re Wands are sufficiently analogous to the instant application to help illustrate this point, as explained in the MPEP (§2164.06(b), pg 2100-195, 8th ed., rev. 2, May 2004):

> (B) In In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), the court reversed the rejection for lack of enablement under 35 U.S.C. 112, first paragraph, concluding that undue experimentation would not be required to practice the invention. The nature of monoclonal antibody technology is such that experiments first involve the entire attempt to make monoclonal hybridomas to determine which ones secrete antibody with the desired characteristics. The court found that the specification provided considerable direction and guidance on how to practice the claimed invention and presented working examples, that all of the methods needed to practice the invention were well known, and that there was a high level of skill in the art at the time the application was filed. Furthermore, the applicant carried out the entire procedure for making a monoclonal antibody against HBsAg three times and each time was successful in producing at least one antibody which fell within the scope of the claims.

In In re Wands, after considering all the factors related to the enablement issue, the court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed

invention." Id., 8 USPQ2d at 1407. In In re Wands, it was not necessary to provide a method to routinely identify *every* monoclonal antibody hybridoma made in any particular production round, or *every possible* monoclonal antibody that could bind the exemplary antigen. Nor was it necessary to produce a working specie after very antibody-making procedure. In fact, in In re Wands, the screening protocol was found sufficiently enabling even though only one antibody was identified after running three procedures.

Analogous to In re Wands, it is not necessary for the specification or the state of the art at the time of the invention describe a protocol where every, or even most, possible variants of the exemplary enzyme of the invention be identified. Because proper legal test is that the scope of enablement must only bear a "reasonable correlation" to the scope of the claims, as in In re Wands, the described screening methods are sufficiently enabling if a reasonable number of claimed species are found, or identified, by the described screening protocols. As declared by Dr. Chaplin, using the teaching of the specification and other protocols known in the art at the time of the invention one skilled in the art could have successfully practiced the methods of the invention without undue experimentation, including identifying enzymes for used in the claimed methods without specific guidance as to which residues to change, or not change. In other words, screening methods known at the time of the invention were sufficiently sophisticated to identify a reasonable number of claimed species even if only a large pool of random sequence variants of the exemplary sequences were made.

Furthermore, also analogous to In re Wands, and as discussed by Dr. Chaplin, the instant specification provided considerable direction and guidance on how to practice the claimed invention and presented working examples. Because the specification provided considerable direction and guidance on how to practice the claimed invention and presented working examples, and all of the methods needed to practice the invention were well known, and there was a high level of skill in the art at the time the application was filed, the instant specification did provide reasonable enablement commensurate with the scope of the claimed invention.

The specification and state of the art did provide guidance as to which residues to change

Regarding the Office's concerns that one skilled in the art needed to have guidance regarding which residues to modify to make species members of the genus of enzymes used in the claimed methods, Applicants respectfully note that, in fact, the specification and the state of the art did provide guidance as to what amino acid substitutions could be made to make the genera of nitrilases of the invention without undue experimentation. For example, the specification expressly describes which particular residues within the exemplary sequences are important such that a nitrilase activity is maintained, and directed the skilled artisan that conservative amino acid substitutions can be made such that the polypeptide essentially retains its functional properties (see page 11, lines 1 to 18, of the final OA):

> ... a "substantially identical" amino acid sequence is a sequence that differs from a reference sequence by one or more conservative or non-conservative amino acid substitutions, deletions, or insertions, particularly when such a substitution occurs at a site that is not the active site of the molecule, and provided that the polypeptide essentially retains its functional properties. A conservative amino acid substitution, for example, substitutes one amino acid for another of the same class (e.g., substitution of one hydrophobic amino acid, such as isoleucine, valine, leucine, or methionine, for another, or substitution of one polar amino acid for another, such as substitution of arginine for lysine, glutamic acid for aspartic acid or glutamine for asparagine). One or more amino acids can be deleted, for example, from a haloalkane dehalogenase polypeptide, resulting in modification of the structure of the polypeptide, without significantly altering its biological activity. For example, amino- or carboxyl-terminal amino acids that are not required for haloalkane dehalogenase biological activity can be removed. Modified polypeptide sequences of the invention can be assayed for haloalkane dehalogenase biological activity by any number of methods, including contacting the modified polypeptide sequence with an haloalkane dehalogenase substrate and determining whether the modified polypeptide decreases the amount of specific substrate in the assay or increases the bioproducts of the enzymatic reaction of a functional haloalkane dehalogenase polypeptide with the substrate.

The specification also provides directed regarding making and screening for members of the genus of polynucleotides and enzymes used in the claimed methods (see, e.g., page 14, line 30 to page 15, line 8):

In another embodiment, the method provides that, the ligation reassembly process is performed systematically, for example in order to generate a systematically compartmentalized library, with compartments that can be screened systematically, e.g., one by one. In other words the invention provides that, through the selective and judicious use of specific nucleic acid building blocks, coupled with the selective and judicious use of sequentially stepped assembly reactions, an experimental design can be achieved where specific sets of progeny products are made in each of several reaction vessels. This allows a systematic examination and screening procedure to be performed. Thus, it allows a potentially very large number of progeny molecules to be examined systematically in smaller groups. (emphasis added)

Accordingly, the specification did provide express guidance as to what amino acid changes could be made, and how to screen for them, to make without undue experimentation the genera of nucleic acids and enzymes used in the claimed methods.

Furthermore, Applicants respectfully aver that, if desired, the skilled artisan could have looked to the art known at the time of the invention for direction as to nitrilase structure and activity, including which bases or amino acid residues in the exemplary sequences could be substituted, deleted or inserted into to obtain other members of the genus of polynucleotides and enzymes of the invention. For example, direction could be found in Kobayashi, et al. (1992) "Primary structure of an aliphatic nitrile-degrading enzyme, aliphatic nitrilase, from *Rhodococcus rhodochrous* K22 and expression of its gene and identification of its active site residue", Biochemistry 31:9000-9007; Kobayashi, et al. (1992) "Nitrilase from *Rhodococcus rhodochrous* J1. Sequencing and overexpression of the gene and identification of an essential cysteine residue", J. Biol. Chem. 267:20746-20751; Kobayashi, et al. (1993) "Nitrilase in biosynthesis of the plant hormone indole-3-acetic acid from indole-3-acetonitrile: cloning of the Alcaligenes gene and site-directed mutagenesis of cysteine residues", Proc. Natl. Acad. Sci. USA 90:247-251; Kobayashi, et al. (1989) "Nitrilase of *Rhodococcus rhodochrous* J1. Purification and characterization", Eur. J. Biochem. 182:349-356; Stevenson, et al., (1992) "Mechanistic and structural studies on Rhodococcus ATCC 39484 nitrilase", Biotechnol. Appl. Biochem. 15:283-302; Kobayashi, et al. (1998) "The catalytic mechanism of amidase also involves nitrile hydrolysis", FEBS Lett. 439:325-328; Stevenson, et al., (1992) "Detection of covalent enzyme-substrate complexes of nitrilase by ion-spray mass spectroscopy", FEBS Lett. 277:112-114; Kobayashi, et al. (1998) "Nitrilase

catalyzes amide hydrolysis as well as nitrile hydrolysis", Biochem. Biophys. Res. Commun. 253:662-666.

In further support of this point, i.e., that the skilled artisan, with the specification, had sufficient guidance as to what base or amino acid residue substitutions could have been made to make the genera of nitrilase sequences of the invention without undue experimentation, Applicants respectfully note that if the skilled artisan desired guidance as to which amino acid residues could be modified to obtain the genera of nitrilase sequences of the invention, that information was, inter alia, readily available in the form of nitrilase sequences known in the art at the time of the invention (Applicants have maintained that it would not have been necessary for one skilled in the art to understand which specific regions of nitrilase structure could be modified to generate – including screen for - the genera of nucleic acids or polypeptides of the invention without undue experimentation). A routine, simple sequence alignment comparison of known nitrilase sequences would have identified regions of identity and dissimilarity to provide guidance to the skilled artisan as to which sequences could be changed, or not changed, to generate structural and/or functional variations of an exemplary nitrilase of the invention. For example, to illustrate this point, Applicants have run a routine, simple sequence alignment comparison of known nitrilase sequences with exemplary sequences of the invention to identify regions of identity and dissimilarity between nitrilases as guidance as to which residue could, or could not, be modified.

The result of this sequence alignment is set forth in Exhibit A (submitted in Applicants' response of Oct. 31, 2005). The alignment compares a random selection of nitrilases known in the art at the time of the invention (nitrilases known prior to Dec. 29, 1999), as summarized in Exhibit B (listing bibliographic information of the prior art sequences in the alignment) (also submitted in Applicants' response of Oct. 31, 2005), with the exemplary nitrilase sequences of the invention, designated as SEQ ID NO:2-09751299 and SEQ ID NO:4-09751299. Regions of common structural identity between polymerases were readily identifiable. The sequence alignment highlights in colors regions of structural identity, with yellow representing regions of common structural identity between all of the nitrilases. Not only are there many regions of common sequence between some or all of the prior art sequences as compared to this invention's exemplary

SEQ ID NO:2 and SEQ ID NO:4, but conserved regions in the alignment compared very closely with the nitrilase catalytic triad glutamate-lysine-cysteine ("EKC"), as reviewed in Pace and Brenner (2001) Genome Biology 2(1):reviews0001.1-0001.9 (Exhibit C) (submitted in Applicants' response of Oct. 31, 2005). This glutamate-lysine-cysteine ("EKC") nitrilase catalytic triad can be seen in, e.g., the nitrilase sequence comparison of Bork (1994) Protein Science 3:1344-1346 (Exhibit D) (submitted in Applicants' response of Oct. 31, 2005). Bork shows an alignment of nitrile bond-cleaving enzymes, i.e., nitrilases. Included in Bork's alignment are four nitrilases (see "Nrl.2_Rhorh; Nrl.1_Rhorh; Nrl.a_Alcfa; Nrl.1b_Klepn, see page 1345), which have the catalytic "EKC" triad of the nitrilase superfamily. Bork, using computer methods for database search and multiple alignment, showed statistically significant sequence similarities between several nitrilases, and that nitrilases are characterized by several conserved motifs, one of which contains an invariant cysteine that is part of the catalytic site in nitrilases, and another is a highly conserved motif including an invariant glutamic acid that might also be involved in catalysis.

Accordingly, the specification and the art provided sufficient guidance to the skilled artisan to reasonably enable him or her how to make and use the genera of nitrilase sequences of the invention without undue experimentation.

Substrates for nitrilases were well known in the art

The Office alleged that "... the predictability of the substrate specificity of SEQ ID NOs:2 and 4 is very low considering the little information disclosed in the instant application and the prior art" (see, e.g., page 5, lines 12 to 14, of paragraph 14, the final OA). However, the Office does state that specification does enable the production of alpha-hydroxy-substituted carboxylic acids and alpha amino acids (see, e.g., page 6, lines 10 to 12, of the final OA). Thus, the instant amendment should address the Office's concerns.

However, Applicants wish to reiterate Dr. Grace DeSantis's Rule 132 expert declaration statements, as submitted with the response of April 11, 2005. Dr. DeSantis declared that the state of the art at the time of the invention and the level of skill of a person of ordinary skill in the art, e.g., determining substrate reactivity, for nitrilase enzymes, was very high, and it would not have

required any knowledge or guidance beyond that provided in the specification as to which substrates were useful with the specific claimed enzymes. Dr. DeSantis declared that at the time of the invention, methods for screening for enzyme substrates were sufficiently comprehensive, routine and predictable at the time of the invention to easily identify which the aldehydes, ketones, cyanide-containing compounds, and ammonium containing compounds to stereoselectively produce an α-substituted carboxylic acid using nitrilases encoded by SEQ ID NO:2 and SEQ ID NO:4. Dr. DeSantis discussed Robertson et al., Applied Environ. Microbiol. 70:2429-36 (2004), declaring that Robertson demonstrates the routine nature of determining substrate specificity, and that such experiments demonstrated the routine nature of screening for substrate reactive to a particular substrate, the predictability of such screening, and ease of determining positive results. Dr. DeSantis declared, in summary, that no undue experimentation would be required and that the specification provided sufficient guidance to one of ordinary skill in the art to make and use the genus of nitrilases.

Additionally, nitrilases and their substrates, and methods for determining the range of substrates for any particular nitrilase enzyme, were known in the art at the time of the invention. Nitrilases were known to have the capacity to be enzymatically active on a variety of substrates. For example, Almatawah (1999) Extremophiles 3:283-291 (Exhibit E) (submitted in Applicants' response of Oct. 31, 2005), characterized a nitrilase that catalyzed the hydrolysis of aliphatic, aromatic, and heterocyclic nitriles with widely varying kcat/KM values, primarily the result of differences in substrate affinity. Kobayashi (1998) Biochem. Biophys. Res. Commun. 253:662-666 (Exhibit F) (submitted in Applicants' response of Oct. 31, 2005), found that nitrilase enzymes also can hydrolyze amides in addition to nitriles using the same active site. Kobayashi (1990) J. Bacteriol. 172:4807-4815 (Exhibit G) (submitted in Applicants' response of Oct. 31, 2005), characterized a nitrilase that preferentially catalyzes the hydrolysis of aliphatic nitriles to the corresponding carboxylic acids and ammonia. Kobayashi (1989) Eur. J. Biochem. 182:349-356 (Exhibit H) (submitted in Applicants' response of Oct. 31, 2005), characterized a nitrilase specific for nitrile groups attached to an aromatic or heteroaromatic ring.

These references collectively support Dr. DeSantis's declaration statements, e.g., that the state of the art at the time of the invention and the level of skill of a person of ordinary skill in the art, e.g., determining substrate reactivity, for nitrilase enzymes, was very high, and it would not have required any knowledge or guidance beyond that provided in the specification as to which substrates were useful with the specific claimed enzymes. These references also collectively support Dr. Chaplin's declaration statements, e.g., that using the teaching of the specification, including the exemplary protocol as set forth the specification and other protocols known in the art at the time of the invention, one skilled in the art at the time of the invention could have successfully practiced the methods of the invention without undue experimentation. These references collectively evidence that protocols for screening for nitrilase activity and nitrilase substrates were well known and routine in the art at the time of the invention.

In light of Applicants' remarks in this and earlier responses, including the submitted expert declaration by Drs. Chaplin and DeSantis, Applicants respectfully submit that the specification provides sufficient enablement to meet the requirements of 35 U.S.C. § 112, first paragraph, and the rejection can be properly withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, it is believed that the Examiner can properly withdraw the rejections of the pending claims, and the application will be in immediate condition for allowance. Accordingly, after entry of the instant amendment, the Examiner is respectfully requested to withdraw the outstanding objections and rejections of the claims and to pass this application to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 564462006600.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at 858 720 5133.

Dated: February 27, 2006

Respectfully submitted,

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